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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/072,381	02/06/2002	Mark A. Goldsmith	GLAD001CON	2681

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EXAMINER	
QIAN, JANICE LI	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/072,381	GOLDSMITH ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-39 and 49-54* is/are pending in the application.

4a) Of the above claim(s) *32,49,50 and 52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-31,33-39,51,53 and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I and species election of homologous CD4, CCR5 and p-TEFb in Paper No. 7 is acknowledged. The restriction was further modified to a linking claim format. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). It is noted that cyclin-T is a subunit of p-TEFb, thus belongs to the elected species. Claims 40-48 have been canceled. Claims 32, 49, 50, and 52 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse. It

Claims 28-31, 33-39, 51, 53, and 54 are under current examination.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 28-31, 33-39, 51, 53, and 54 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 11, 13 of U.S. Patent No. 6,372,956.

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims of the cited patent encompass the instant claims.

The claims of the cited patent and instant claims are each drawn to a transgenic rat whose genome comprises a first stably integrated transgenic nucleotide sequence encoding a human CD4 and a second stably integrated transgenic nucleotide sequence encoding a human chemokine receptor, which is selected from a group consisting of CCR5.

The product of the present application and the cited patent differ one from the other in that the cited patent does not particularly recite a third stably integrated transgenic nucleotide sequence encoding a polypeptide that interacts with an HIV sequence. However, the subject matter is fully disclosed in the specification (see particularly column 13, lines 22-37).

Claims 53 and 54 are drawn to a method for making the tri-transgenic rats, which is also fully disclosed in the specification of the cited patent (paragraph bridging columns 13 and 14).

Accordingly, the claimed rats in the cited patent and the present application are obvious variants. Therefore, the inventions as claimed are co-extensive.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-31, 33-39, 51, 53, and 54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings, or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

Claims 28 and 53 recite a transgene nucleotide sequence encoding a polypeptide that interacts with an HIV sequence. Given the broadest reasonable

interpretation, claims encompass numerous polypeptides (a genus of), which interact with an HIV sequence and there is no limitation on the structure or function of the polypeptide or the HIV sequences. However, the specification fails to provide an adequate disclosure for the genus of the claimed invention in terms of distinguishing characteristics of the genus. The only polypeptide disclosed that meets claim limitation is a p-TEFb complex comprising CDK9 and cyclin T subunits. Considering all possible *polypeptides that would interact with an HIV sequence*, their modes of operation, and various phenotypes of the rats resulting from the tri-transgene expression, the disclosed p-TEFb is not a representative species of the genus. The court has stated, "IN CHEMICAL CASE WHERE APPLICANT DISCLOSES THAT ONE SPECIES OF A CLASS OF CHEMICALS WILL ACCOMPLISH CERTAIN PURPOSE WITHOUT NAMING ANY OTHERS OF CLASS TO WHICH IT BELONGS OR WITHOUT SO DESCRIBING THE SPECIES AND ITS MODE OF OPERATION AS TO CALL ATTENTION TO FACT THAT OTHER MEMBERS OF CLASS ARE ITS EQUIVALENTS AND WILL PERFORM SAME FUNCTIONS, HE IS NOT ENTITILED TO BROADER SCOPE OF DISCLOSED INVENTION BY CLAIMING WHOLE GROUP EVEN THOUGH THOSE SKILLED IN ART MAY KNOW THAT IN SOME RESPECTS AT LEAST DIFFERENT MEMBERS OF GROUP ARE EQUIVALENTS; CERTAIN MEMBERS OF WELL-DEFINED GROUP OF CHEMICALS MAY BE EQUIVALENTS FOR ONE PURPOSE AND NOT EQUIVALENT FOR ANOTHER. (In re Soll, 97 F.2d623, 38 USPQ 189 (CCPA 1938). Therefore, the specification fails to provide an adequate description to teach the structures, the identifying characteristics, and the structure-function relationship of the genus of polypeptides and rats expressing these polypeptides, and accordingly does not provide a reasonable guide for those seeking to practice the invention.

The Revised Interim Guidelines state "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (Column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (Column 2, page 71436).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, the specification does not provide an adequate written description of the claimed invention in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 28-31, 33-39, 51, 53, and 54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation

would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

These claims are drawn to using a polypeptide that interacts with an HIV sequence for making a tri-transgenic rat, however, as indicated *supra* in the written description section, the specification fails to provide an adequate description for the broad classes of polypeptides encompassed by the claims, and the function and utility of the resulting rats. Since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed genus, p-TEFb alone is insufficient to describe the genus. One cannot extrapolate the teachings of the specification to the scope of the claims because the skilled artisan cannot envision the detailed structures of the polypeptides encompassed by these claims, and how to use the rats with various phenotypes, thus except the p-TEFb, one would not know how to use the invention without first carrying out undue experimentation to determine the phenotype and utility for the genus of rats. Therefore, in view of the limited guidance, the lack of predictability of the art, and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Claims 28-39, 51, 53, and 54 are further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in

such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims are drawn to a transgenic rat whose genome comprises three stably integrated transgenic nucleotide sequences, preferably CD4, CCR5, and p-TEFb, wherein the three transgenes are constructed into one vector and operably linked to one (any) promoter, which results in the polypeptides to be preferentially expressed which results in HIV adhesion and infection of T-cells.

The specification teaches making different lines of transgenic rats expressing either CD4 or CCR5 with a vector comprising a single transgene, i.e. either CD4 or CCR5, operably linked to a T cell-specific or CD4 enhancer/promoter/intron region (figs. 2 & 3), mating different lines of rats and selecting for rats with a bi-transgene phenotype, whereby the transgene is preferentially expressed in T cells (examples 4 & 5). However, the specification fails to make a three-transgene construct operably linked to any non-T cell-specific promoter that could be preferentially expressed in T cells, nor producing a transgenic rat with the tri-transgene vector. Accordingly, fails to provide an enabling disclosure to support the full scope of the claims. This is because although the technique for making transgenic animals has become routine in the relevant art, the resulting genotype and phenotype varies significantly depending on the genes being manipulated, and the animals being used. *Logan and Sharma* (Clin Exp Pharmacol Physiol 1999 Dec;26:1020-25) teach that the type of construct is essential for the success of making a transgenic animal with a predetermined phenotype, "THE CHALLENGE IN THE DEVELOPMENT OF TRANSGENE IS NOT IN THIS PROCESS, BUT IN THE DESIGN OF THE

CONSTRUCT THAT WILL ALLOW FOR THE EXPRESSION OF THE GENE OF INTEREST IN THE DESIRED CELL TYPE AT AN APPROPRIATE LEVEL", "PROBLEMS WITH OBTAINING EXPRESSION OF TRANSGENES IN AMINALS HAVE BEEN RELATED TO THE INABILITY TO ROUTINELY OBTAIN HIGH LEVELS OF EXPRESSION, ESPECIALLY OVER MULTIPLE GENERATIONS, AND THE OBSERVATION OF VARIEGATED EXPRESSION, WHEREBY NOT ALL CELLS IN AN ORGAN WILL EXPRESS THE GENE" (Emphasis added). The art of transgenic animal product has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have within their cells cellular mechanisms which prevent expression of the transgene, such as DNA methylation or deletion from the genome (*Kappell et al*, Current Opinion in Biotechnology 1992;3, 549, col. 2, parag. 2). *Mullins et al* (Hypertension 1993;22, page 631, col. 1, parag. 1, lines 14-17) states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into difference species of animal has been reported to given divergent phenotypes. The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (*Houdebine* J. Biotech. 1994;34, page 281). "The position effect" and unidentified control elements also are recognized to cause aberrant expression (*Wall,* Theriogenology 1996;45, 61, parag. 2, line 9 to page 62, line 3). Well-regulated transgenic expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (*Cameron*, Molec. Biol. 1997;7, page 256, col. 1 -2, bridg. parag.). Factors influencing low expression, or the lack their of, are not affected by copy number and such effects are

seen in lines of transgenic mice made with the same construct (*Cameron*, Molec. Biol. 1997;7, page 256, lines 3-9). These factors, thus, are copy number independent and integration site dependent, emphasizing the role the integration site plays on expression of the transgene (*Cameron*, Molec. Biol. 1997;7, page 256, lines 10-13). Further, *Sigmund* (Arteroscler. Throm. Vasc. Biol. 2000;20, page 1426, col. 1, paragraph 1, lines 1-7) states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene effects expression, and thus the observed phenotype. With regard to the importance of promoter selection, *Niemann* (Transg. Res. 1997 ;7, page 73, col. 2, parag. 2, line 12 to page 73, col. 1, line 4) states that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to the pig, the other compatible with pig health. While, the intent is not to say that transgenic animals of a particular phenotype can never be made, the intent is to provide art taught reasoning as to why the instant claims are not enabled. Thus, the phenotype resulting from random insertion of a three-transgene vector driven by any promoter would expect to be varied and unpredictable.

Claims 53 and 54 require transfecting any cell with the three-transgene vector, introducing the cell into a blastocyst and generating a fetus expressing the three transgenes. The method encompasses nuclear transfer and selection for target cells. However, the nuclear transfer technology is still under-development, and highly inefficient with respect to the generated phenotype and well being of the animal. With respect to somatic cell cloning, *Denning* (Nat Biotech 2001;19:559-562) teach the

difficulties of cell targeting, "A SUBSTANTIAL NUMBER OF COLONIES WITH ONLY TARGETED CELLS SENESCED BEFORE THEY COULD BE PREPARED FOR NUCLEAR TRANSFER. THE HIGH ATTRITION RATE OF TARGETED CLONAL POPULATIONS SUITABLE FOR NUCLEAR TRANSFER REPRESENTS ONE OF THE MAJOR HURDLES OF GENE TARGETING IN PRIMARY SOMATIC CELLS" (left column, page 560). *Yanagimachi* (Mol Cell Endocrinol 2002;187:241-8) teaches that high percentage of cloned fetuses died in uterus reflecting the challenge in the art, "CLONING EFFICIENCY-AS DETERMINED BY THE PROPORTION OF LIVE OFFSPRING DEVELOPED FROM ALL OOCYTES THAT RECEIVED DONOR CELL NUCLEI-IS LOW REGARDLESS OF THE CELL TYPE (INCLUDING, EMBRYONIC STEM CELLS) AND ANIMAL SPECIES USED. IN ALL ANIMALS EXCEPT OF JAPANESE BLACK BEEF CATTLE, THE VAST MAJORITY OF CLONED EMBRYOS PERISH BEFORE REACHING FULL TERM" (Abstract), and "THUS FAR, CLONED OFFSPRING THAT SURVIVED BIRTH AND REACHED ADULTHOOD WERE THE EXCEPTION RATHER THAN THE RULE (page 243, left column, emphasis added). *Yanagimachi* goes on to teach, "THIS LOW EFFICIENCY OF CLONING SEEMS TO BE DUE LARGELY TO FAULTY EPIGENETIC REPROGRAMMING OF DONOR CELL NUCLEI AFTER TRANSFER INTO RECIPIENT OOCYTES. CLONED EMBRYOS WITH MAJOR EPIGENETIC ERRORS DIE BEFORE OR SOON AFTER IMPLANTATION" (abstract). *Wells et al* (Trends Biotechnol 2003:21:428-32) teach that the continuous loss of clones throughout pregnancy and high mortality during the perinatal period raise serious animal welfare concerns and these losses can mostly be attributed to faulty epigenetic reprogramming of the donor cell genome, resulting in major dysregulation of gene expression (paragraph bridging left & right column in page 1). Considering these art known hurdles, and lack of reduction in making a tri-transgenic rat having the desired phenotype, and unavailability of p-TEFb transgenic rat, the claimed method or the tri-transgenic rat do not appear to be enabled in the absence of evidence to the

contrary. MPEP teaches, "WHEN CONSIDERING THE FACTORS RELATING TO A DETERMINATION OF NON-ENABLEMENT, IF ALL THE OTHER FACTORS POINT TOWARD ENABLEMENT, THEN THE ABSENCE OF WORKING EXAMPLES WILL NOT BY ITSELF RENDER THE INVENTION NON-ENABLED." "LACK OF A WORKING EXAMPLE, HOWEVER, IS A FACTOR TO BE CONSIDERED, ESPECIALLY IN A CASE INVOLVING AN UNPREDICTABLE AND UNDEVELOPED ART." (MPEP 2164.02, 03) Accordingly, taking as a whole the state of the art, the levels of the skilled in the art, the disclosure of the specification, and the lack of working, it would have required undue experimentation for reproducibly using the claimed method and making the claimed rat.

With respect to the ES cells encompassed by the claims in making the transgenic rat, embryonic stem (ES) cells must be available to carry out the method. The state of the art is such that ES cell technology is generally limited to the mouse system at present, and that only "putative" ES cells exist for other species (see Moreadith *et al.*, **J. Mol. Med.**, 1997, p. 214, S*ummary*). Note that "putative" ES cells lack a demonstration of the cell to give rise to germline tissue or the whole animal, a demonstration which is an art-recognized property of ES cells. Moreadith *et al.* supports this observation as they discuss the historical perspective of mouse ES cells as follows: "THE STAGE WAS SET-ONE COULD GROW NORMAL, DIPLOID ES CELLS IN CULTURE FOR MULTIPLE PASSAGES WITHOUT LOSS OF THE ABILITY TO CONTRIBUTE TO NORMAL DEVELOPMENT. FURTHERMORE, THE CELLS CONTRIBUTED TO THE DEVELOPMENT OF GAMETES AT A HIGH FREQUENCY (GERMLINE COMPETENCE) AND THE HAPLOID GENOMES OF THESE CELLS WERE TRANSMITTED TO THE NEXT GENERATION. THUS, THE INTRODUCTION OF MUTATIONS IN THESE CELLS OFFERED THE POSSIBILITY OF PRODUCING MICE WITH A PREDETERMINED GENOTYPE." Such a demonstration has not been provided by the specification or the prior or post-filing art with regard to the generation of rat ES cells,

which can give rise to the germline tissue of a developing animal. In addition, prior to the time of filing, *Mullins et al.* (Journal of Clinical Investigation, 1996) report that "ALTHOUGH TO DATE CHIMERIC ANIMALS HAVE BEEN GENERATED FROM SEVERAL SPECIES INCLUDING THE PIG, IN NO SPECIES OTHER THAN THE MOUSE HAS GERMLINE TRANSMISSION OF AN ES CELL BEEN SUCCESSFULLY DEMONSTRATED." (page S38, column 1, first paragraph). As the claims are drawn to methods involving the manipulation of rat embryonic stem (ES), and particularly since the subject matter of the specification and the claimed invention encompasses the use of such cells for the generation of a transgenic animal, the state of the art supports that only mouse ES cells were available for use for production of transgenic mice.

A further unpredictable factor comes from the structure and function of the p-TEFb. The claims are drawn to using a subunit of the p-TEFb, however, the state of the art teaches that various subunits of the human p-TEFb complex may play distinct roles at multiple stages to mediate Tat activation of HIV-1 transcription elongation as a whole. The art of record is silent and the specification fails to teach whether a subunit of p-TEFb alone would achieve what is the goal of the invention (*Zhou et al*, EMBO J 1998;17:3681-91, see particularly the conclusion in abstract). Moreover, the art of record teaches the effect of attenuating or deleting p-TEFb, the effect of over-expressing such was unknown. In fact, *Martin-Serrano et al* (J Virol 2002;76:208-19) teach, the levels of cyclin T1 in unstimulated primary lymphocytes matches the levels of activated T cells, and it does not limit HIV tat function. Thus, the phenotype of the

claimed tri-transgenic rat is unpredictable with respect to whether it could have an enhanced ability for HIV-1 infection as compared to the bi-transgenic rat.

Claims also encompass transgenic rats heterozygous for the three transgenes, however, the transgenic rat would not express the proteins of interest if the gene is an autosomal dominant, and the resulting rats would not have a phenotype, thus, indistinctable from a wild-type rat. The specification fails to teach otherwise, thus, fails to provide an enabling disclosure to support the full scope of the invention.

Accordingly, in view of numerous unknown factors and hurdles in the art as discussed foregoing, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for the claimed invention. Although the instant specification contemplates making a tri-transgenic rat functionally expressing human CD4, CCR5, and p-TEFb with a vector comprising three transgenes operably linked to any promoter, it is not enabled for its full scope because determination of the phenotype of the resulting rat is not predictable until they are actually made and used, hence resulting in a trial and error situation. Therefore, the general knowledge and levels of skill in the art do not supplement the omitted description, because specific, not general guidance is what is needed.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942 (571-272-0730, after the Office relocation in January, 2004). The examiner can normally be reached on 9:30 am - 6 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JANICE LI
PATENT EXAMINER

Q. Janice Li
Patent Examiner
Art Unit 1632

QJL
December 22, 2003